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(54) Title: INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

(57) Abstract

The present invention is directed to compounds which inhibit farnesyl-protein transferase (FTase) and the farnesylation of the oncogene protein Ras. The invention is further directed to chemotherapeutic compositions containing the compounds of this invention and methods for inhibiting farnesyl-protein transferase and the farnesylation of the oncogene protein Ras.

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TITLE OF THE INVENTION

INHIBITORS OF FARNESYL-PROTEIN TRANSFERASE

BACKGROUND OF THE INVENTION

The Ras proteins (Ha-Ras, Ki4a-Ras, Ki4b-Ras and N-Ras) are part of a signalling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation. Biological and biochemical studies of Ras action indicate that Ras functions like a G-regulatory protein. In the inactive state, Ras is bound to GDP. Upon growth factor receptor activation Ras is induced to exchange GDP for GTP and undergoes a conformational change. The GTP-bound form of Ras propagates the growth stimulatory signal until the signal is terminated by the intrinsic GTPase activity of Ras, which returns the protein to its inactive GDP bound form (D.R. Lowy and D.M. Willumsen, *Ann. Rev. Biochem. 62*:851-891 (1993)). Mutated *ras* genes (Ha-*ras*, Ki4a-*ras*, Ki4b-*ras* and N-*ras*) are found in many human cancers, including colorectal carcinoma, exocrine pancreatic carcinoma, and myeloid leukemias. The protein products of these genes are defective in their GTPase activity and constitutively transmit a growth stimulatory signal.

Ras must be localized to the plasma membrane for both normal and oncogenic functions. At least 3 post-translational modifications are involved with Ras membrane localization, and all 3 modifications occur at the C-terminus of Ras. The Ras C-terminus contains a sequence motif termed a "CAAX" or "Cys-Aaa^1-Aaa^2-Xaa" box (Cys is cysteine, Aaa is an aliphatic amino acid, the Xaa is any amino acid) (Willumsen *et al., Nature 310*:583-586 (1984)). Depending on the specific sequence, this motif serves as a signal sequence for the enzymes farnesyl-protein transferase or geranylgeranyl-protein transferase, which catalyze the alkylation of the cysteine residue of the CAAX motif with a C_{15} or C_{20} isoprenoid, respectively. (S. Clarke., *Ann. Rev. Biochem. 61*:355-386 (1992); W.R. Schafer and J. Rine, *Ann. Rev. Genetics 30*:209-237 (1992)). The Ras protein is one of several proteins that are known to undergo post-translational farnesylation.

Other farnesylated proteins include the Ras-related GTP-binding proteins such as Rho, fungal mating factors, the nuclear lamins, and the gamma subunit of transducin. James, et al., *J. Biol. Chem. 269*, 14182 (1994) have identified a peroxisome associated protein Pxf which is also farnesylated. James, et al., have also suggested that there are farnesylated proteins of unknown structure and function in addition to those listed above.

Inhibition of farnesyl-protein transferase has been shown to block the growth of Ras-transformed cells in soft agar and to modify other aspects of their transformed phenotype. It has also been demonstrated that certain inhibitors of farnesyl-protein transferase selectively block the processing of the Ras oncoprotein intracellularly (N.E. Kohl *et al.*, *Science*, *260*:1934-1937 (1993) and G.L. James *et al.*, *Science*, *260*:1937-1942 (1993). Recently, it has been shown that an inhibitor of farnesyl-protein transferase blocks the growth of *ras*-dependent tumors in nude mice (N.E. Kohl *et al.*, *Proc. Natl. Acad. Sci U.S.A.*, *91*:9141-9145 (1994) and induces regression of mammary and salivary carcinomas in *ras* transgenic mice (N.E. Kohl *et al.*, *Nature Medicine*, 1:792-797 (1995).

Indirect inhibition of farnesyl-protein transferase *in vivo* has been demonstrated with lovastatin (Merck & Co., Rahway, NJ) and compactin (Hancock *et al.*, *ibid*; Casey *et al.*, *ibid*; Schafer *et al.*, *Science 245*:379 (1989)). These drugs inhibit HMG-CoA reductase, the rate limiting enzyme for the production of polyisoprenoids including farnesyl pyrophosphate. Farnesyl-protein transferase utilizes farnesyl pyrophosphate to covalently modify the Cys thiol group of the Ras CAAX box with a farnesyl group (Reiss *et al.*, *Cell*, *62*:81-88 (1990); Schaber *et al.*, *J. Biol. Chem.*, *265*:14701-14704 (1990); Schafer *et al.*, *Science*, *249*:1133-1139 (1990); Manne *et al.*, *Proc. Natl. Acad. Sci USA*, *87*:7541-7545 (1990)). Inhibition of farnesyl pyrophosphate biosynthesis by inhibiting HMG-CoA reductase blocks Ras membrane localization in cultured cells. However, direct inhibition of farnesyl-protein transferase would be more specific and attended by fewer side

effects than would occur with the required dose of a general inhibitor of isoprene biosynthesis.

Inhibitors of farnesyl-protein transferase (FPTase) have been described in two general classes. The first are analogs of farnesyl diphosphate (FPP), while the second class of inhibitors is related to the protein substrates (e.g., Ras) for the enzyme. The peptide derived inhibitors that have been described are generally cysteine containing molecules that are related to the CAAX motif that is the signal for protein prenylation. (Schaber *et al.*, *ibid*; Reiss *et. al.*, *ibid*; Reiss *et al.*, *PNAS*, *88*:732-736 (1991)). Such inhibitors may inhibit protein prenylation while serving as alternate substrates for the farnesyl-protein transferase enzyme, or may be purely competitive inhibitors (U.S. Patent 5,141,851, University of Texas; N.E. Kohl *et al.*, *Science*, *260*:1934-1937 (1993); Graham, et al., *J. Med. Chem.*, *37*, 725 (1994)). In general, deletion of the thiol from a CAAX derivative has been shown to dramatically reduce the inhibitory potency of the compound. However, the thiol group potentially places limitations on the therapeutic application of FPTase inhibitors with respect to pharmacokinetics, pharmacodynamics and toxicity. Therefore, a functional replacement for the thiol is desirable.

It has recently been reported that farnesyl-protein transferase inhibitors are inhibitors of proliferation of vascular smooth muscle cells and are therefore useful in the prevention and thereapy of arteriosclerosis and diabetic disturbance of blood vessels (JP H7-112930).

It has recently been disclosed that certain tricyclic compounds which optionally incorporate a piperidine moiety are inhibitors of FPTase (WO 95/10514, WO 95/10515 and WO 95/10516). Imidazole-containing inhibitors of farnesyl protein transferase have also been disclosed (WO 95/09001 and EP 0 675 112 A1).

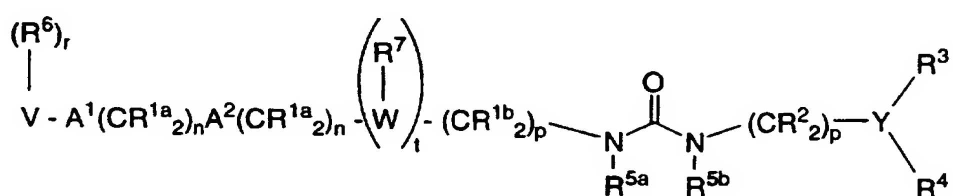
It is, therefore, an object of this invention to develop peptidomimetic compounds that do not have a thiol moiety, and that will inhibit farnesyl-protein transferase and thus, the post-translational farnesylation of proteins. It is a further object of this invention to

develop chemotherapeutic compositions containing the compounds of this invention and methods for producing the compounds of this invention.

SUMMARY OF THE INVENTION

The present invention comprises small molecule peptidomimetic urea-containing compounds which inhibit the farnesyl-protein transferase. The instant compounds lack a thiol moiety and thus offer unique advantages in terms of improved pharmacokinetic behavior in animals, prevention of thiol-dependent chemical reactions, such as rapid autoxidation and disulfide formation with endogenous thiols, and reduced systemic toxicity. Further contained in this invention are chemotherapeutic compositions containing these farnesyl transferase inhibitors and methods for their production.

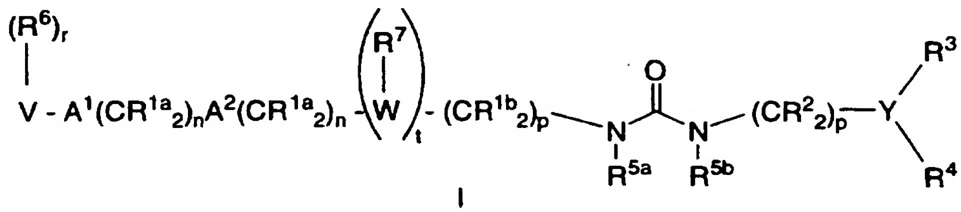
The compounds of this invention are illustrated by the formula I:



I

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are useful in the inhibition of farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. In a first embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula I:



I

wherein:

R^{1a}, R^{1b} and R^2 are independently selected from:

a) hydrogen,

b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-,

c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)$-NR^8-;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $CF_3(CH_2)_nO$-, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^{5a} and R^{5b} are independently selected from:

a) hydrogen,

b) unsubstituted or substituted aryl,

c) unsubstituted or substituted heterocyclic,

d) unsubstituted or substituted C_3-C_{10} cycloalkyl, and

e) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl,

unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-$C(NH)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^8OC(O)NH$-;

R^7 is selected from:

a) hydrogen,
b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-C-(NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-,

$-C(O)-$, $-C(O)NR^8-$, $-NR^8C(O)-$, O, $-N(R^8)-$, $-S(O)_2N(R^8)-$, $-N(R^8)S(O)_2-$, or $S(O)_m$;

V is selected from:

a) hydrogen,
b) heterocycle,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

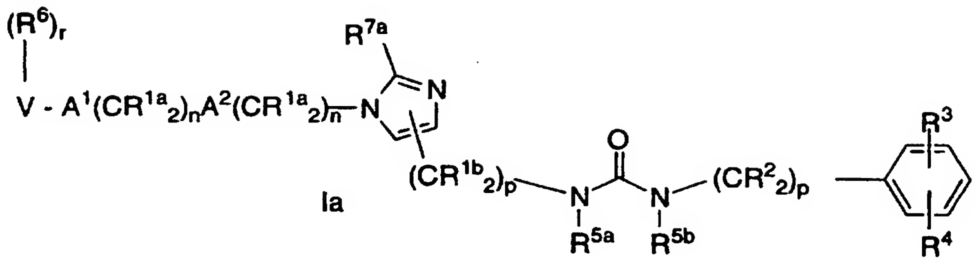
W is a heterocycle;

Y is aryl or heteroaryl;

m is	0, 1 or 2;
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
r is	0 to 5, provided that r is 0 when V is hydrogen; and
t is	0 or 1;

or the pharmaceutically acceptable salts thereof.

A preferred embodiment of the compounds of this invention are illustrated by the formula Ia:



Ia

wherein:

R^{1a} and R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or -$N(R^8)_2$;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^{5a} and R^{5b} are independently selected from:

a) hydrogen,

and

b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-,

$(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-C(NH)-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{7a} is hydrogen or methyl;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -$C(O)NR^8$-, O, -$N(R^8)$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

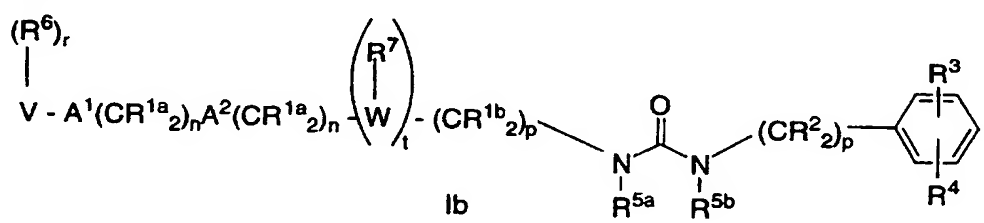
e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
r is 0 to 5, provided that r is 0 when V is hydrogen; and

or the pharmaceutically acceptable salts thereof.

A second preferred embodiment of the compounds of this invention are illustrated by the formula Ib:



Ib

wherein:

R^{1a} and R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or -$N(R^8)_2$;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or

unsubstituted aryl and substituted or unsubstituted heterocycle;

R^{5a} and R^{5b} are independently selected from:

a) hydrogen,

and

b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^7 is selected from: hydrogen and C_1-C_6 alkyl;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^8$-, O, $-N(R^8)$-, or $S(O)_m$;

V is selected from:

a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and

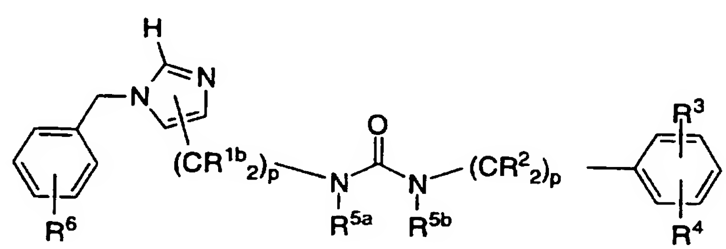
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle selected from pyrrolidinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

m is	0, 1 or 2;
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
r is	0 to 5, provided that r is 0 when V is hydrogen; and
t is	1;

or the pharmaceutically acceptable salts thereof.

In a more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula Ic:



Ic

wherein:

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or -$N(R^8)_2$;

R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^{5a} and R^{5b} are independently selected from:

a) hydrogen,
and
b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

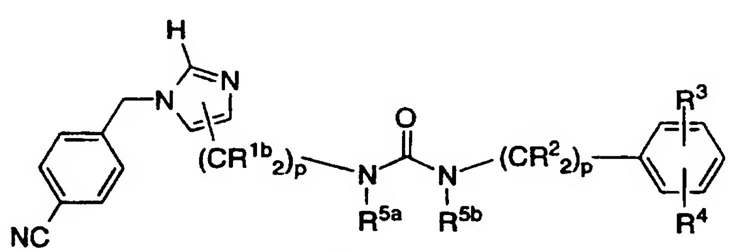
R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or the pharmaceutically acceptable salts thereof.

In a second more preferred embodiment of this invention, the inhibitors of farnesyl-protein transferase are illustrated by the formula Id:



Id

wherein:

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or -$N(R^8)_2$;

R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^{5a} and R^{5b} are independently selected from:

a) hydrogen,

and

b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

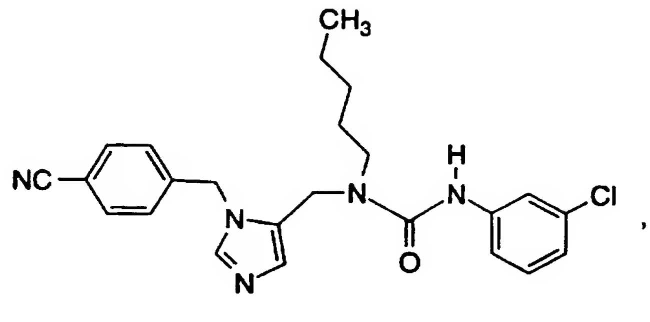
R^9 is independently selected from C_1-C_6 alkyl and aryl;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

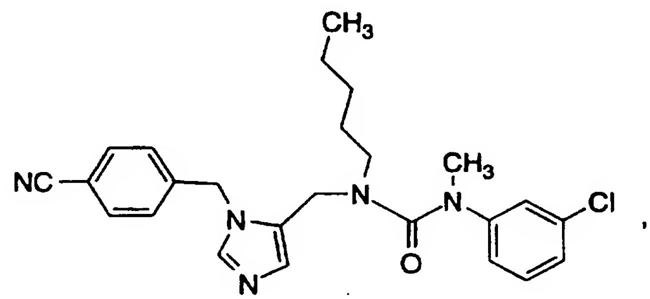
or the pharmaceutically acceptable salts thereof.

Specific examples of the compounds of the invention are:

N-(3-chlorophenyl)-*N'*-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N'*-(*n*-pentyl)urea hydrochloride (1)



N-(3-chlorophenyl)-*N*-methyl-*N'*-[1-(4-cyanobenzyl)-5-imidazolyl-methyl]-*N'*-(*n*-pentyl)urea hydrochloride (**8**)



or the pharmaceutically acceptable salts thereof.

The compounds of the present invention may have asymmetric centers and occur as racemates, racemic mixtures, and as individual diastereomers, with all possible isomers, including optical isomers, being included in the present invention. When any variable (e.g. aryl, heterocycle, R^{1a}, R^2 etc.) occurs more than one time in any constituent, its definition on each occurence is independent at every other occurence. Also, combinations of substituents/or variables are permissible only if such combinations result in stable compounds.

As used herein, "alkyl" is intended to include both branched and straight-chain saturated aliphatic hydrocarbon groups having the specified number of carbon atoms; "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen

bridge. "Halogen" or "halo" as used herein means fluoro, chloro, bromo and iodo.

As used herein, "aryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic. Examples of such aryl elements include phenyl, naphthyl, tetrahydronaphthyl, indanyl, biphenyl, phenanthryl, anthryl or acenaphthyl.

The term heterocycle or heterocyclic, as used herein, represents a stable 5- to 7-membered monocyclic or stable 8- to 11-membered bicyclic heterocyclic ring which is either saturated or unsaturated, and which consists of carbon atoms and from one to four heteroatoms selected from the group consisting of N, O, and S, and including any bicyclic group in which any of the above-defined heterocyclic rings is fused to a benzene ring. The heterocyclic ring may be attached at any heteroatom or carbon atom which results in the creation of a stable structure. Examples of such heterocyclic elements include, but are not limited to, azepinyl, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolidinyl, imidazolinyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolidinyl, isothiazolyl, isothiazolidinyl, morpholinyl, naphthyridinyl, oxadiazolyl, 2-oxoazepinyl, 2-oxopiperazinyl, 2-oxopiperdinyl, 2-oxopyrrolidinyl, piperidyl, piperazinyl, pyridyl, pyrazinyl, pyrazolidinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydrofuryl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiazolyl, thiazolinyl, thienofuryl, thienothienyl, and thienyl.

As used herein, "heteroaryl" is intended to mean any stable monocyclic or bicyclic carbon ring of up to 7 members in each ring, wherein at least one ring is aromatic and wherein from one to four carbon atoms are replaced by heteroatoms selected from the group

consisting of N, O, and S. Examples of such heterocyclic elements include, but are not limited to, benzimidazolyl, benzisoxazolyl, benzofurazanyl, benzopyranyl, benzothiopyranyl, benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, cinnolinyl, dihydrobenzofuryl, dihydrobenzothienyl, dihydrobenzothiopyranyl, dihydrobenzothiopyranyl sulfone, furyl, imidazolyl, indolinyl, indolyl, isochromanyl, isoindolinyl, isoquinolinyl, isothiazolyl, naphthyridinyl, oxadiazolyl, pyridyl, pyrazinyl, pyrazolyl, pyridazinyl, pyrimidinyl, pyrrolyl, quinazolinyl, quinolinyl, quinoxalinyl, tetrahydroisoquinolinyl, tetrahydroquinolinyl, thiazolyl, thienofuryl, thienothienyl, and thienyl.

Lines drawn into the ring systems from substituents (such as from R^3, R^4 etc.) indicate that the indicated bond may be attached to any of the substitutable ring carbon atoms.

Preferably, R^{1a}, R^{1b} and R^2 are independently selected from: hydrogen, $-N(R^8)_2$, $R^8C(O)NR^8-$ or C_1-C_6 alkyl unsubstituted or substituted by $-N(R^8)_2$, R^8O- or $R^8C(O)NR^8-$.

Preferably, R^3 and R^4 are independently selected from: hydrogen, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m-$, CN, NO_2, $R^8{}_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8-$ and C_1-C_6 alkyl.

Preferably, R^{5a} and R^{5b} are independently selected from hydrogen or C_1-C_6 alkyl substituted with hydrogen, $R^9S(O)_m-$, CF_3- or an unsubstituted or substituted aryl group.

Preferably, R^6 is selected from: hydrogen, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m-$, CN, NO_2, $R^8{}_2N-C(NR^8)-$, $R^8C(O)-$, $R^8OC(O)-$, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8-$ and C_1-C_6 alkyl.

Preferably, R^7 is hydrogen or methyl. Most preferably, R^7 is hydrogen.

Preferably, R^8 is selected from H, C_1-C_6 alkyl and benzyl.

Preferably, A^1 and A^2 are independently selected from: a bond, $-C(O)NR^8-$, $-NR^8C(O)-$, O, $-N(R^8)-$, $-S(O)_2N(R^8)-$ and-$N(R^8)S(O)_2-$.

Preferably, V is selected from hydrogen, heterocycle and aryl. Most preferably, V is phenyl.

Preferably, Y is selected from phenyl, pyridyl, furyl and thienyl. Most preferably, Y is phenyl.

Preferably, n, p and r are independently 0, 1, or 2.

Preferably t is 1.

The pharmaceutically acceptable salts of the compounds of this invention include the conventional non-toxic salts of the compounds of this invention as formed, e.g., from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like: and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pamoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxy-benzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isethionic, trifluoroacetic and the like.

It is intended that the definition of any substituent or variable (e.g., R^{1a}, Z, n, etc.) at a particular location in a molecule be independent of its definitions elsewhere in that molecule. Thus, $-N(R^8)_2$ represents -NHH, $-NHCH_3$, $-NHC_2H_5$, etc. It is understood that substituents and substitution patterns on the compounds of the instant invention can be selected by one of ordinary skill in the art to provide compounds that are chemically stable and that can be readily synthesized by techniques known in the art, as well as those methods set forth below, from readily available starting materials.

The pharmaceutically acceptable salts of the compounds of this invention can be synthesized from the compounds of this invention which contain a basic moiety by conventional chemical methods. Generally, the salts are prepared either by ion exchange chromatography or by reacting the free base with stoichiometric amounts or with an excess of the desired salt-forming inorganic or organic acid in a suitable solvent or various combinations of solvents.

Reactions used to generate the compounds of this invention are prepared by employing reactions as shown in Schemes 1-13, in addition to other standard manipulations such as ester hydrolysis, cleavage of protecting groups, etc., as may be known in the literature or exemplified in the experimental procedures. Substituents R' and R'CH_2-, as shown in the Schemes, represent the substituents R^8, R^9 and others, depending on the compound of the instant invention that is being synthesized. The variable p' represents p-1.

These reactions may be employed in a linear sequence to provide the compounds of the invention or they may be used to synthesize fragments which are subsequently joined by the alkylation reactions described in the Schemes.

Synopsis of Schemes 1-13:

The requisite intermediates are in some cases commercially available, or can be prepared according to literature procedures, for the most part. Schemes 1-3 illustrates the synthesis of one of the preferred embodiments of the instant invention, wherein the variable W is present as a imidazolyl moiety that is substituted with a suitably substituted benzyl group. Substituted protected imidazole alkanols II can be prepared by methods known in the art, such as those described by F. Schneider, *Z. Physiol. Chem.*, 3:206-210 (1961) and C.P. Stewart, *Biochem. Journal*, 17:130-133(1923). Benzylation and deprotection of the imidazole alkanol provides intermediate III which can be oxidized to the corresponding aldehyde IV. Aldehyde IV can then be reductively coupled to a suitably substituted amine to provide intermediate V.

Scheme 2 illustrates other methods of preparing amine intermediates. Thus, the alkanol II may be converted to the corresponding amine VI via the azide. Alternatively, if the appropriately substituted protected amine, such as a protected histamine VII, is available, that reagent may be ring alkylated to provide the intermediate amine VIII.

Amines such as those illustrated in Schemes 1 and 2 may be reacted with a suitably substituted isocyanate IX to provide the instant

compound X. Compound X can be selectively N-alkylated under standard conditions, such as those illustrated, to provide the instant compound XI.

Schemes 4-7 illustrate syntheses of suitably substituted alkanols useful in the syntheses of the instant compounds wherein the variable W is present as a pyridyl moiety. Similar synthetic strategies for preparing alkanols that incorporate other heterocyclic moieties for variable W are also well known in the art.

The isocyanate IX can be reacted with a variety of other amines, such as XII, as shown in Scheme 8. The product XIII can be deprotected to give the instant compound XIV. The compound XIV is isolated in the salt form, for example, as a trifluoroacetate, hydrochloride or acetate salt, among others. Compound XIV can further be selectively protected to obtain XV which can subsequently be reductively alkylated with a second aldehyde, such as XVI, to obtain XVII. Removal of the protecting group, and conversion to cyclized products such as the dihydroimidazole XIX can be accomplished by literature procedures.

As shown in Scheme 9, a bis-protected aldehyde XX may be reacted with a suitable Grignard reagent to provide the secondary alcohol XXI. Subsequent protection and reductive deprotection provides the primary alcohol XXII. This alcohol can then be converted to the corresponding amine by the techniques illustrated in Schemes 1-2 above. Amine XXIII may then be reacted with isocyanate IX to provide the carbamate XXIV. Removal of the protecting groups then provides the instant compound XXV In addition, a fully deprotected amino alcohol XXVII can be reductively alkylated (under conditions described previously) with a variety of aldehydes to obtain secondary amines, such as XXVIII (Scheme 10), or tertiary amines.

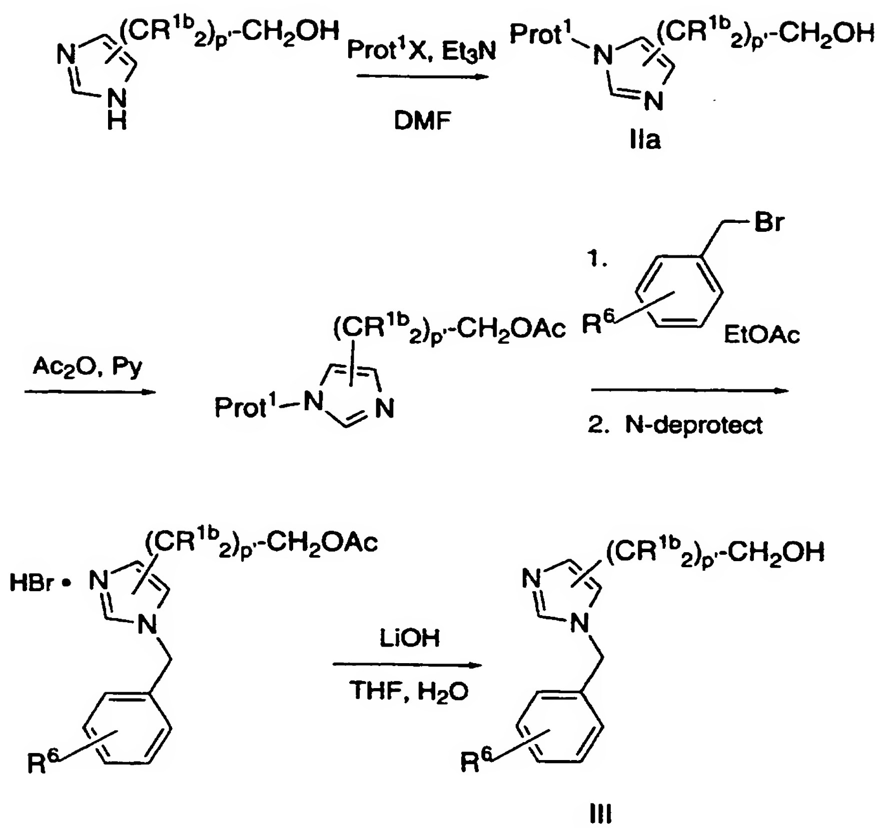
The Boc protected amino alcohol XXIX can also be utilized to synthesize 2-aziridinylmethylureas such as XXX (Scheme 11). Treating XXIX with 1,1'-sulfonyldiimidazole and sodium hydride in a solvent such as dimethylformamide can lead to the formation of

aziridine XXX. The aziridine can be reacted with a nucleophile, such as a thiol, in the presence of base to yield the ring-opened product XXXI.

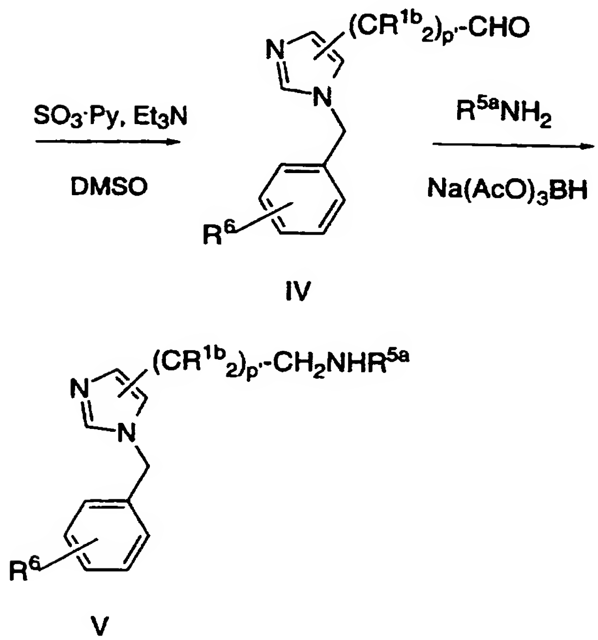
In addition, the isocyanate IX can be reacted with aldehydes derived from amino acids such as O-alkylated tyrosines, according to standard procedures, to obtain compounds such as XXXVII, as shown in Scheme 12. When R' is an aryl group, XXXVII can first be hydrogenated to unmask the phenol, and the amine group deprotected with acid to produce XXXVIII. Alternatively, the amine protecting group in XXXVII can be removed, and O-alkylated phenolic amines such as IXL produced.

Schemes 13 illustrates an alternate preparation of the instant compounds. As shown in Scheme 13, the isocyanate XL is formed first and is then treated with the suitably substituted aniline such as XLI to provide the instant compound X.

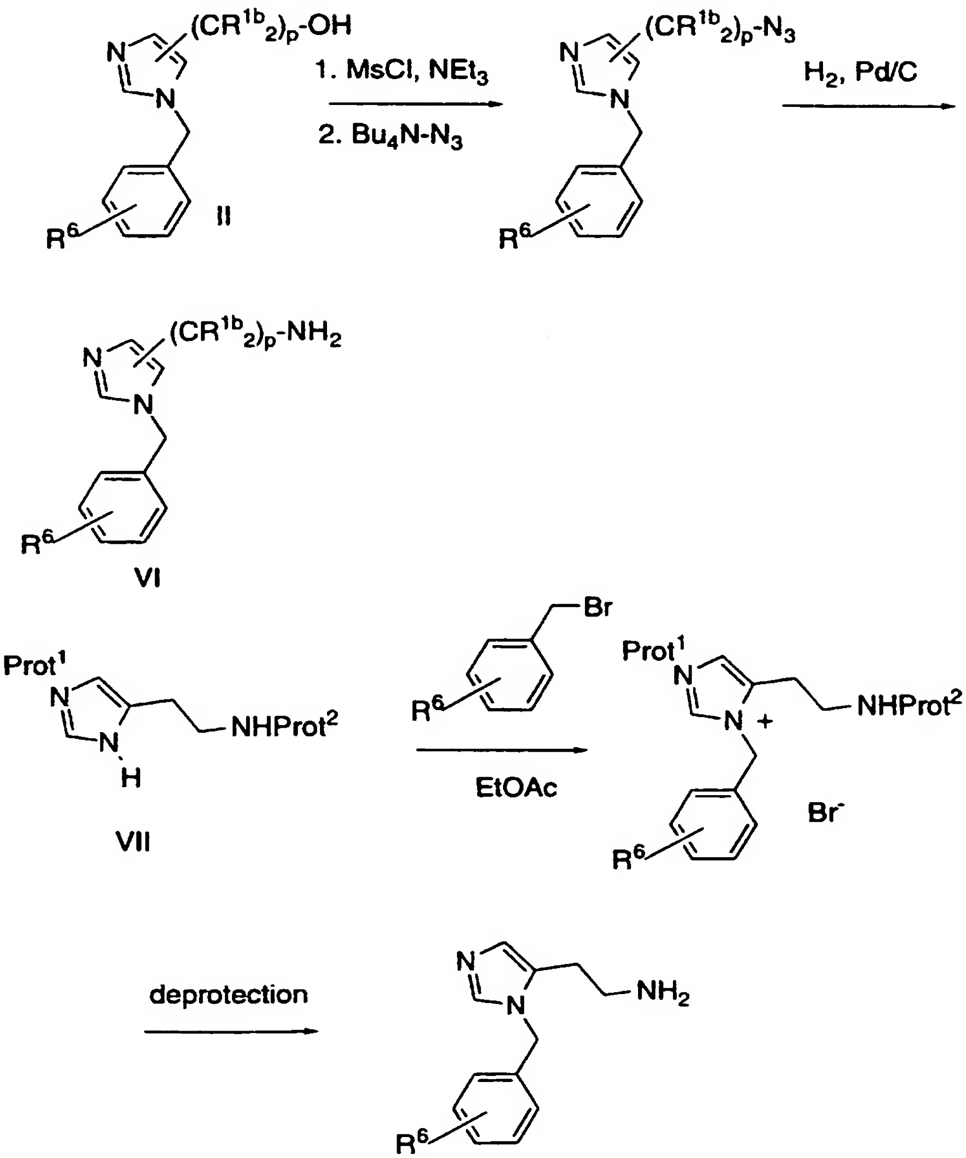
SCHEME 1


(CR1b2)p'-CH2OH
Prot1X, Et3N
DMF
Prot1
IIa
Ac2O, Py
(CR1b2)p'-CH2OAc
1.
Br
R6
EtOAc
2. N-deprotect
HBr •
LiOH
THF, H2O
III

SCHEME 1 (continued)

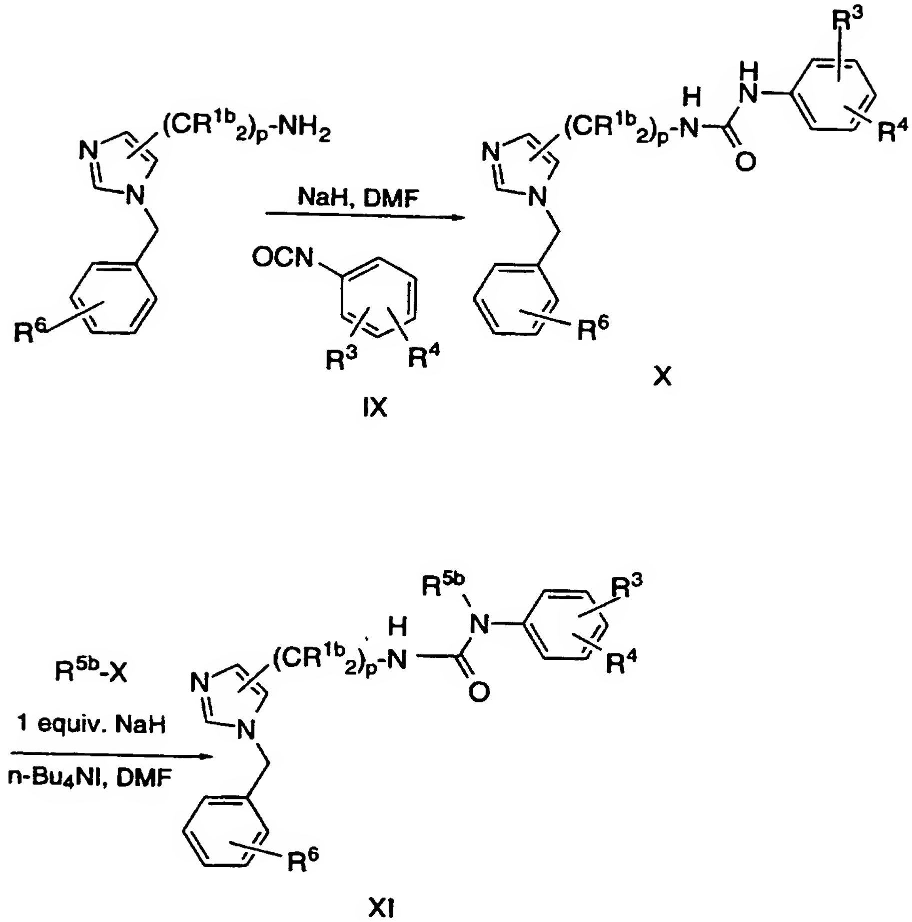


SCHEME 2

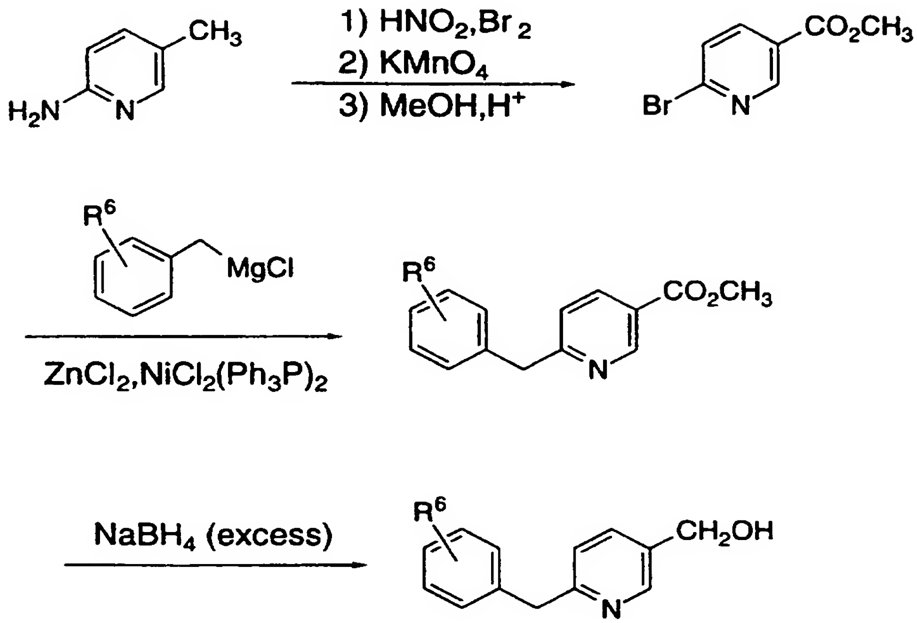


VIII

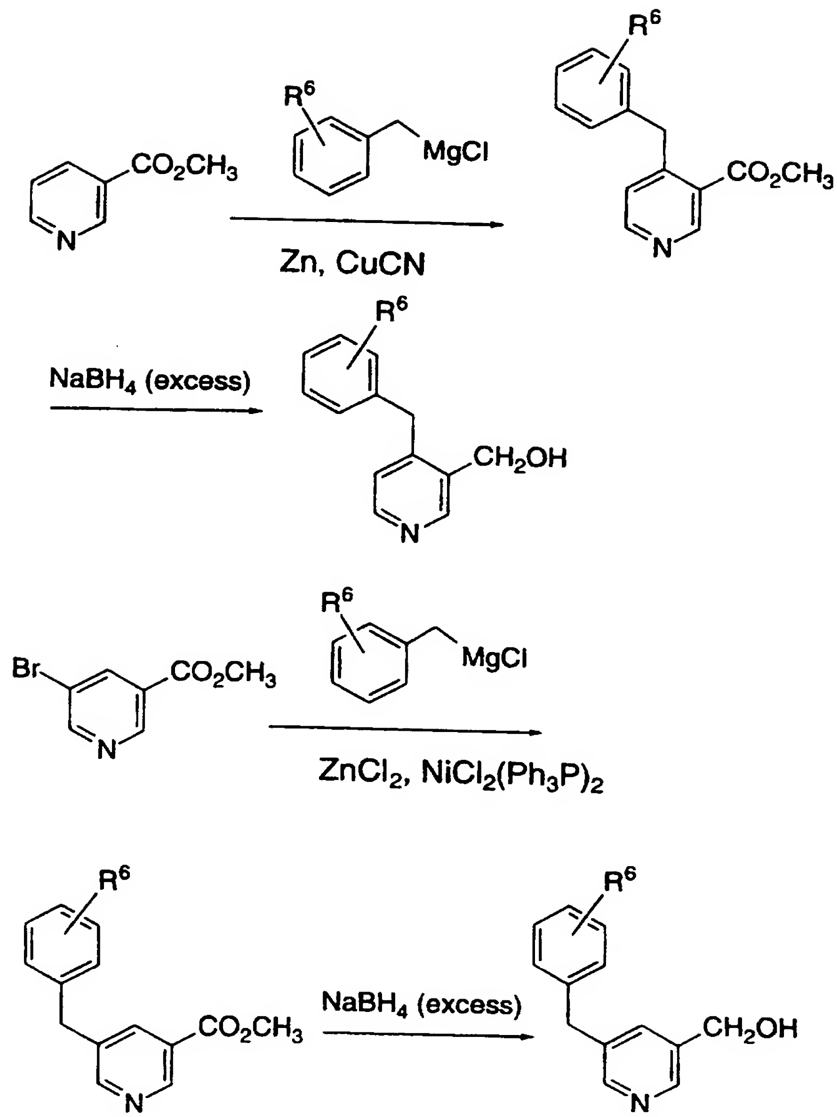
SCHEME 3


(CR1b2)p-NH2
N
N
R6
NaH, DMF
OCN
R3
R4
IX
R3
H
N
H
(CR1b2)p-N
O
R4
R6
X
R5b-X
1 equiv. NaH
n-Bu4NI, DMF
R5b
H
N
(CR1b2)p-N
O
R3
R4
R6
XI

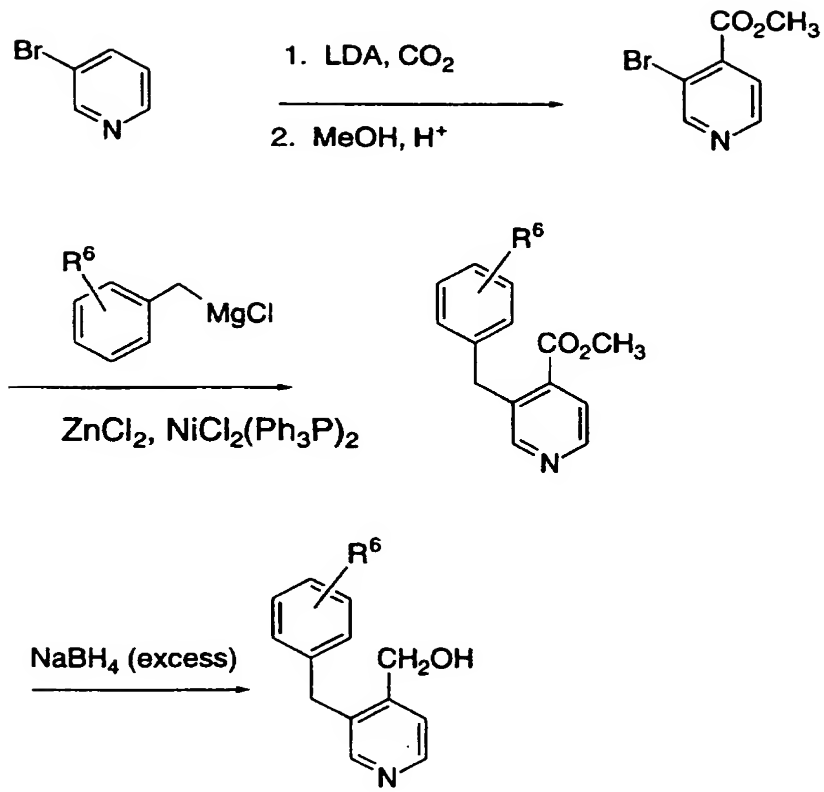
SCHEME 4


CH3
H2N
N
1) HNO2,Br 2
2) KMnO4
3) MeOH,H+
CO2CH3
Br
N
R6
MgCl
ZnCl2,NiCl2(Ph3P)2
R6
CO2CH3
N
NaBH4 (excess)
R6
CH2OH
N

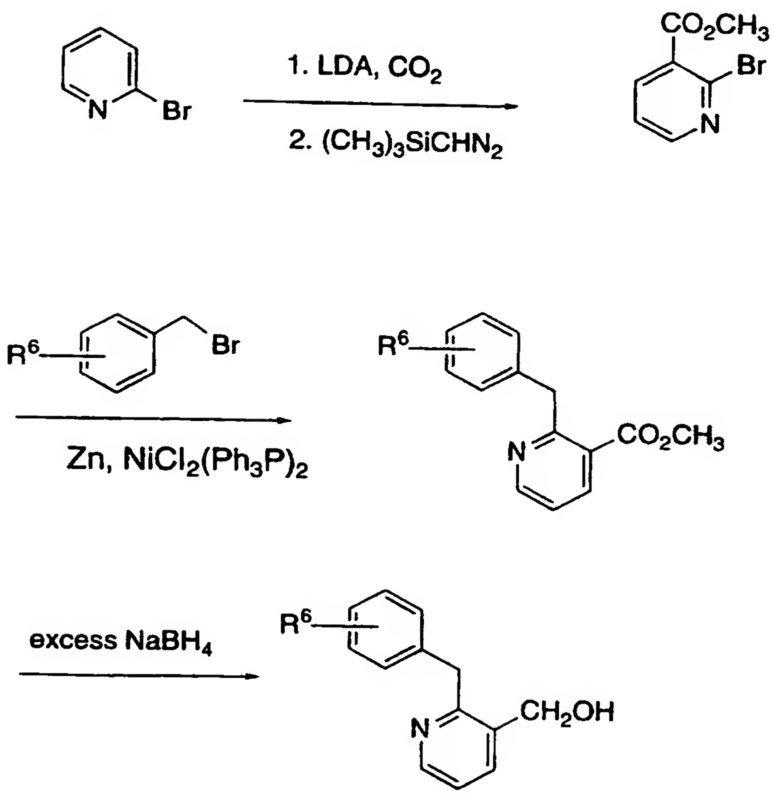
SCHEME 5



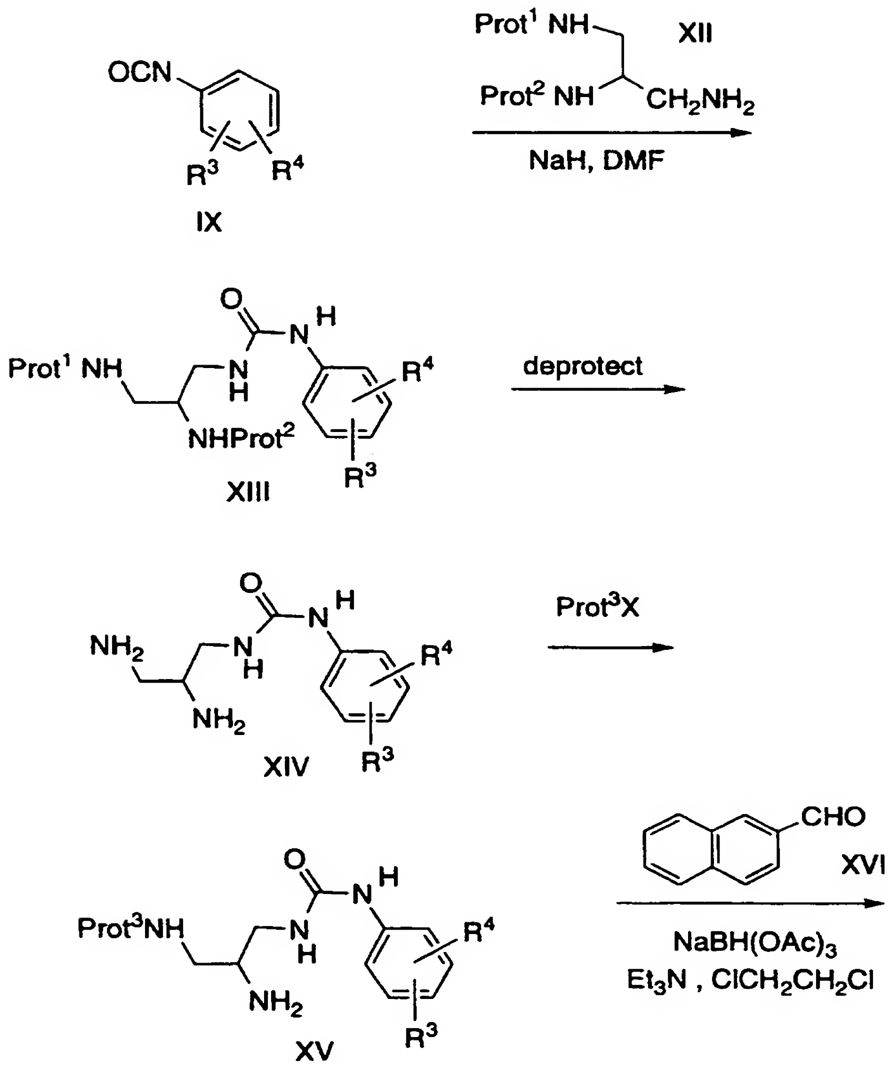
SCHEME 6


Br
N
1. LDA, CO2
2. MeOH, H+
CO2CH3
Br
N
R6
MgCl
ZnCl2, NiCl2(Ph3P)2
R6
CO2CH3
N
NaBH4 (excess)
R6
CH2OH
N

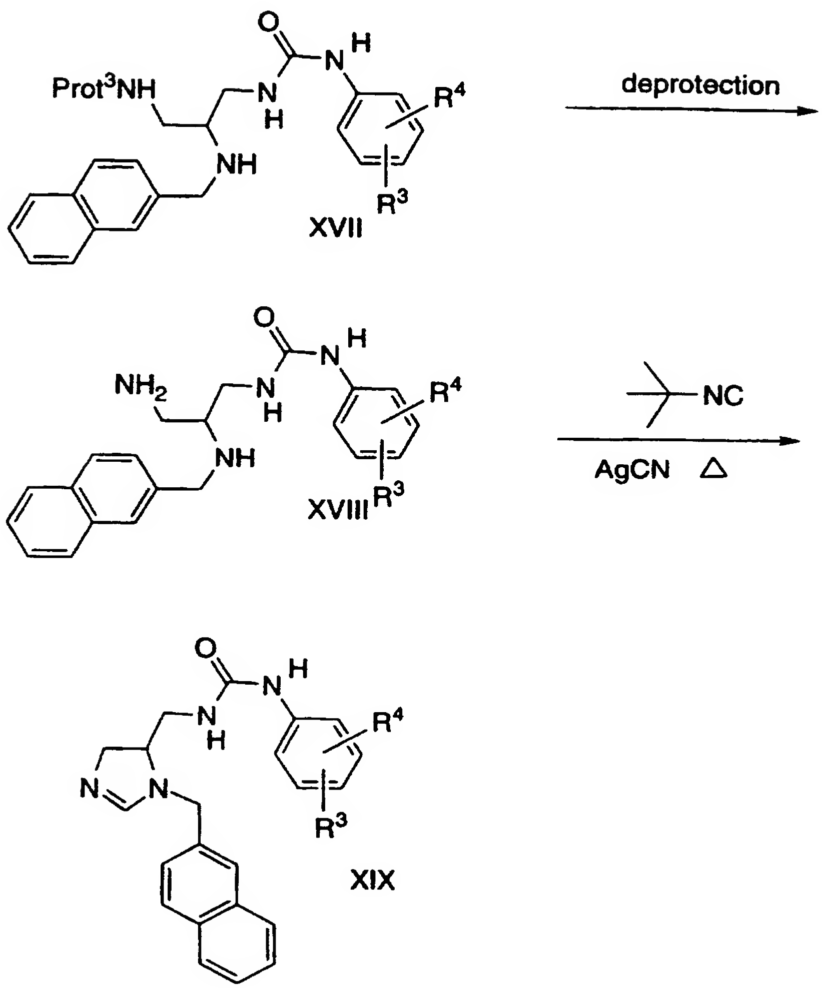
SCHEME 7


Br
1. LDA, CO_2
2. $(CH_3)_3SiCHN_2$
CO_2CH_3
Br
N
R^6
Br
Zn, $NiCl_2(Ph_3P)_2$
CO_2CH_3
excess $NaBH_4$
CH_2OH

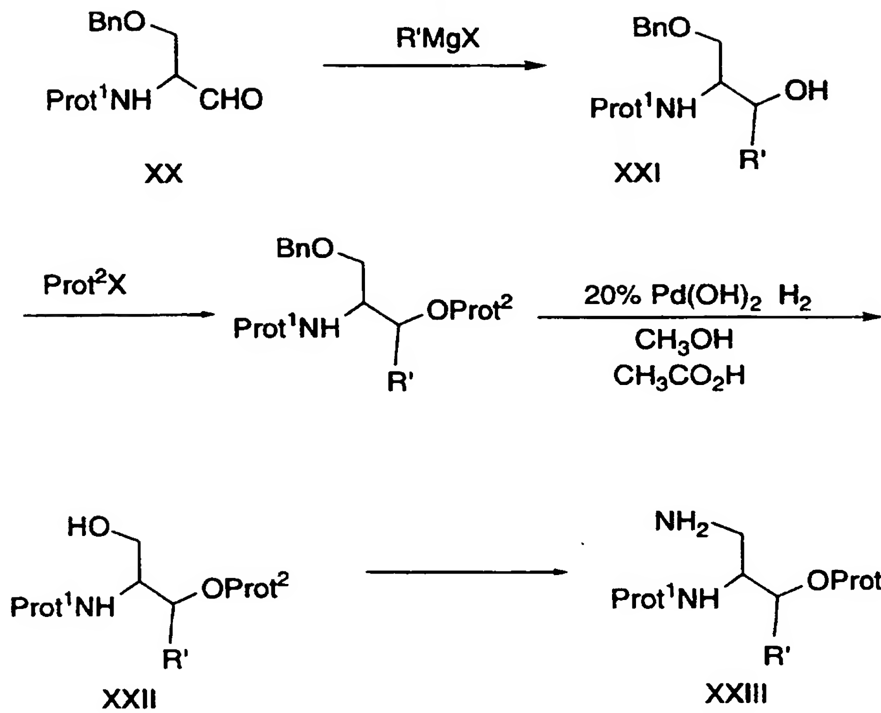
SCHEME 8


OCN
R3
R4
IX
Prot1 NH
XII
Prot2 NH
CH2NH2
NaH, DMF
Prot1 NH
NHProt2
XIII
deprotect
NH2
XIV
Prot3X
Prot3NH
XV
CHO
XVI
NaBH(OAc)3
Et3N, ClCH2CH2Cl

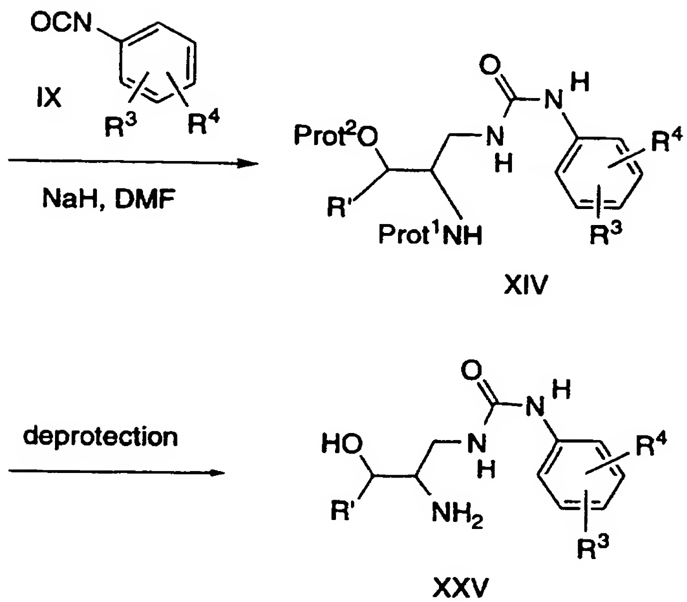
SCHEME 8 (continued)



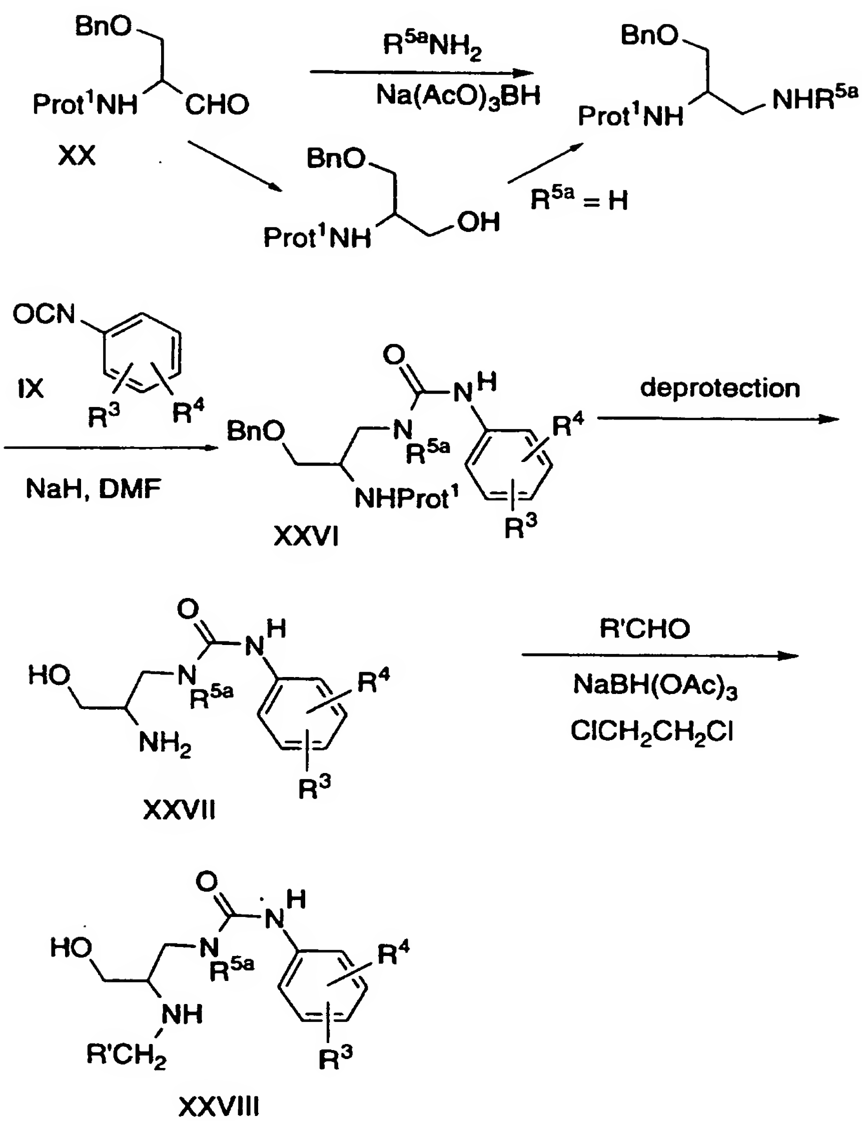
SCHEME 9


BnO
Prot¹NH
CHO
XX
R'MgX
BnO
Prot¹NH
OH
R'
XXI
Prot²X
BnO
Prot¹NH
OProt²
R'
20% Pd(OH)₂ H₂
CH₃OH
CH₃CO₂H
HO
Prot¹NH
OProt²
R'
XXII
NH₂
Prot¹NH
OProt²
R'
XXIII

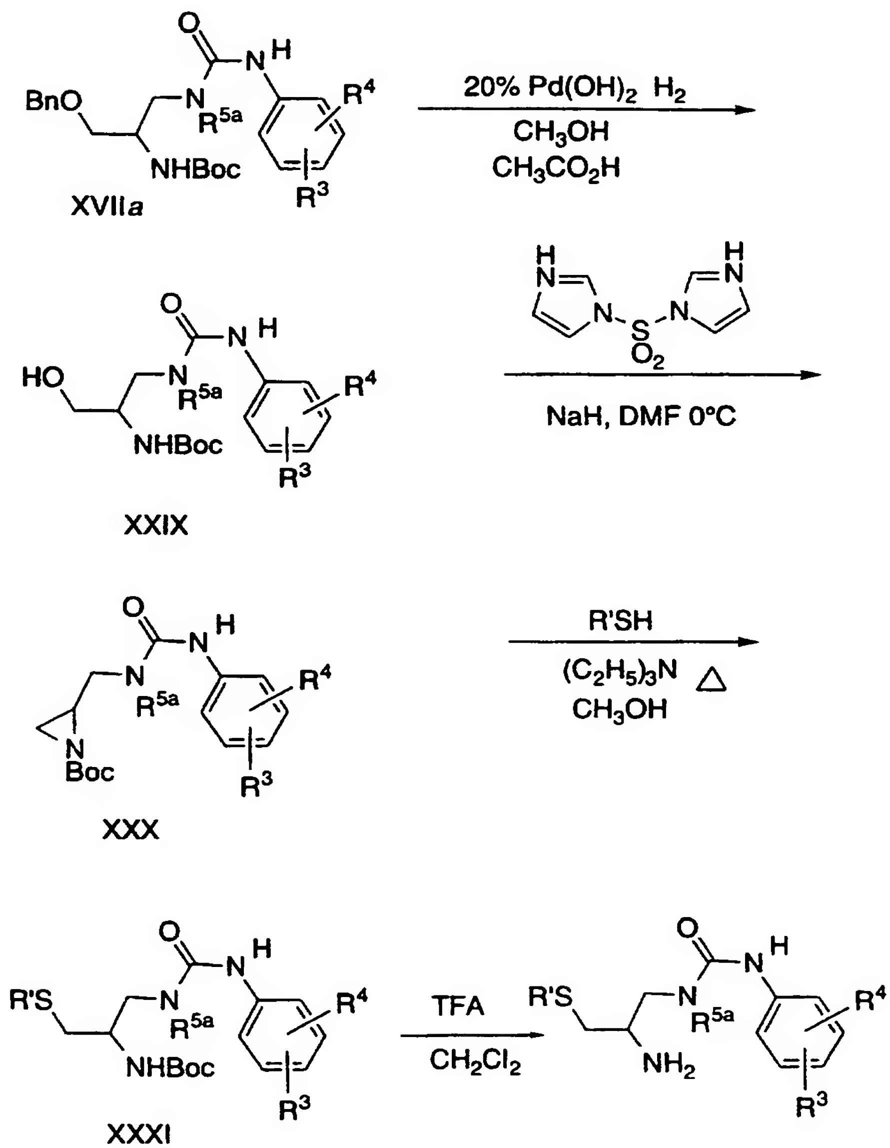
SCHEME 9 (continued)



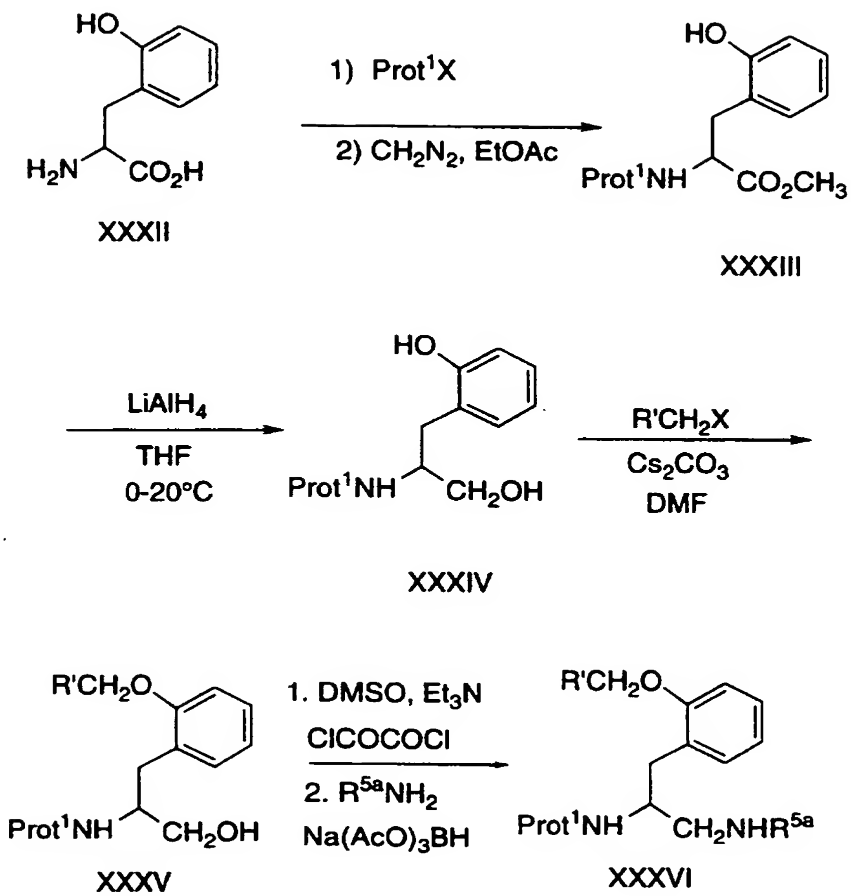
SCHEME 10



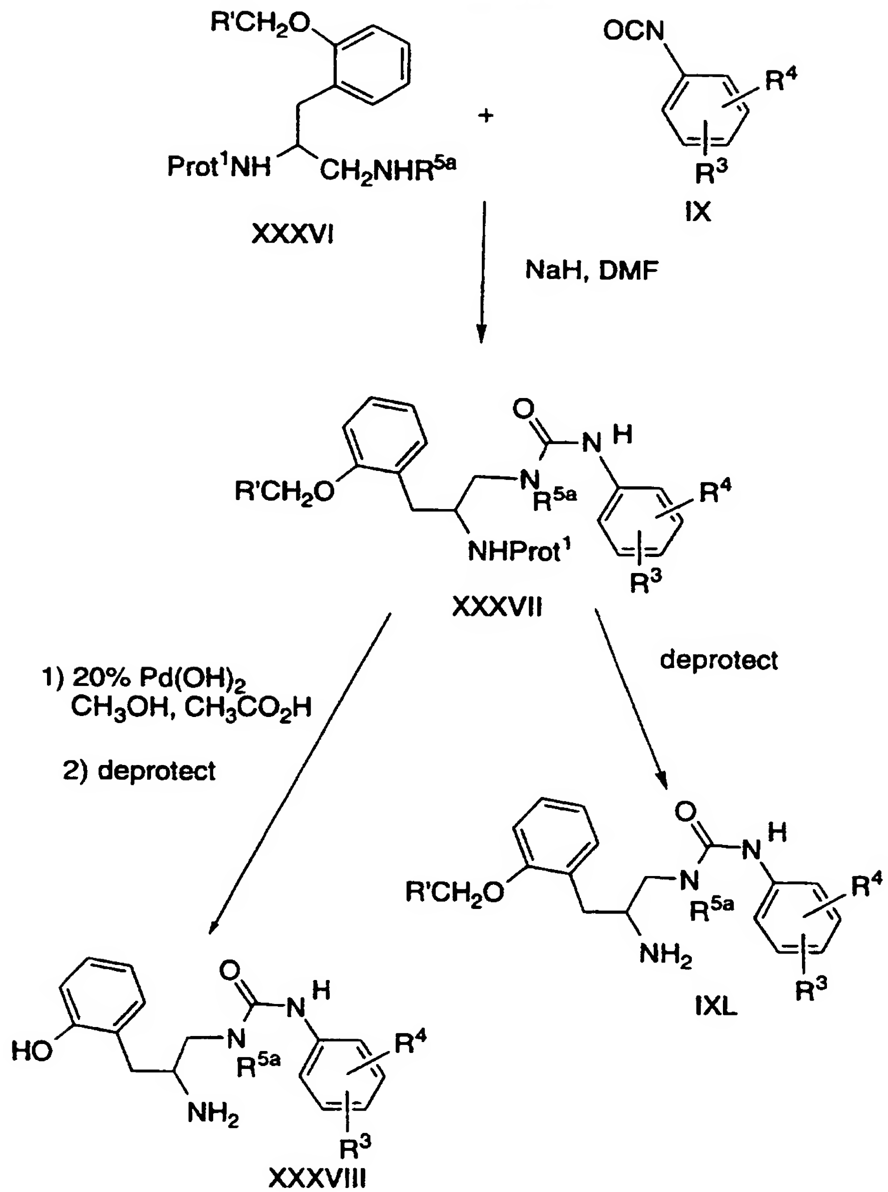
SCHEME 11


BnO
NHBoc
R5a
R4
R3
XVIIa
20% Pd(OH)2 H2
CH3OH
CH3CO2H
HO
XXIX
NaH, DMF 0°C
Boc
XXX
R'SH
(C2H5)3N
CH3OH
R'S
XXXI
TFA
CH2Cl2
NH2

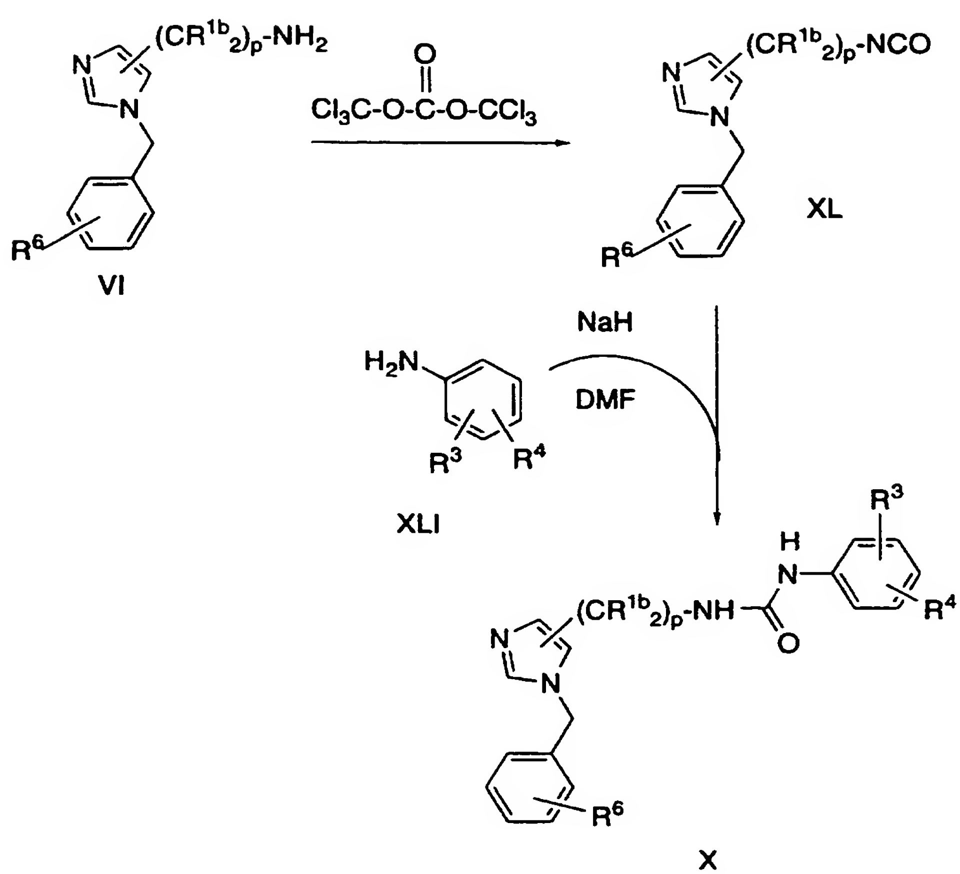
SCHEME 12


HO
H_2N
CO_2H
XXXII
1) Prot^{1}X
2) CH_2N_2, EtOAc
HO
Prot^{1}NH
CO_2CH_3
XXXIII
$LiAlH_4$
THF
0-20°C
HO
Prot^{1}NH
CH_2OH
XXXIV
R'CH_2X
Cs_2CO_3
DMF
R'CH_2O
Prot^{1}NH
CH_2OH
XXXV
1. DMSO, Et_3N
ClCOCOCl
2. $R^{5a}NH_2$
$Na(AcO)_3BH$
R'CH_2O
Prot^{1}NH
CH_2NHR^{5a}
XXXVI

SCHEME 12 (continued)



SCHEME 13


(CR^{1b}$_2$)$_p$-NH$_2$
N
N
R^6
VI
O
Cl$_3$C-O-C-O-CCl$_3$
(CR^{1b}$_2$)$_p$-NCO
XL
NaH
DMF
H$_2$N
R^3
R^4
XLI
H
N
(CR^{1b}$_2$)$_p$-NH
O
X

The instant compounds are useful as pharmaceutical agents for mammals, especially for humans. These compounds may be administered to patients for use in the treatment of cancer. Examples of the type of cancer which may be treated with the compounds of this invention include, but are not limited to, colorectal carcinoma, exocrine pancreatic carcinoma, myeloid leukemias and neurological tumors. Such tumors may arise by mutations in the *ras* genes themselves, mutations in the proteins that can regulate Ras formation (i.e., neurofibromen (NF-1), neu, scr, ab1, lck, fyn) or by other mechanisms.

The compounds of the instant invention inhibit farnesyl-protein transferase and the farnesylation of the oncogene protein Ras. The instant compounds may also inhibit tumor angiogenisis, thereby affecting the growth of tumors (J. Rak et al. *Cancer Research*, 55:4575-4580 (1995)). Such anti-angiogenisis properties of the instant compounds may also be useful in the treatment of certain forms of blindness related to retinal vascularization.

The compounds of this invention are also useful for inhibiting other proliferative diseases, both benign and malignant, wherein Ras proteins are aberrantly activated as a result of oncogenic mutation in other genes (i.e., the Ras gene itself is not activated by mutation to an oncogenic form) with said inhibition being accomplished by the administration of an effective amount of the compounds of the invention to a mammal in need of such treatment. For example, a component of NF-1 is a benign proliferative disorder.

The instant compounds may also be useful in the treatment of certain viral infections, in particular in the treatment of hepatitis delta and related viruses (J.S. Glenn et al. *Science*, 256:1331-1333 (1992).

The compounds of the instant invention are also useful in the prevention of restenosis after percutaneous transluminal coronary angioplasty by inhibiting neointimal formation (C. Indolfi et al. *Nature Medicine*, 1:541-545(1995).

The instant compounds may also be useful in the treatment and prevention of polycystic kidney disease (D.L. Schaffner et al.

American Journal of Pathology, 142:1051-1060 (1993) and B. Cowley, Jr. et al.*FASEB Journal*, 2:A3160 (1988)).

The compounds of this invention may be administered to mammals, preferably humans, either alone or, preferably, in combination with pharmaceutically acceptable carriers or diluents, optionally with known adjuvants, such as alum, in a pharmaceutical composition, according to standard pharmaceutical practice. The compounds can be administered orally or parenterally, including the intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical routes of administration.

For oral use of a chemotherapeutic compound according to this invention, the selected compound may be administered, for example, in the form of tablets or capsules, or as an aqueous solution or suspension. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch, and lubricating agents, such as magnesium stearate, are commonly added. For oral administration in capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents may be added. For intramuscular, intraperitoneal, subcutaneous and intravenous use, sterile solutions of the active ingredient are usually prepared, and the pH of the solutions should be suitably adjusted and buffered. For intravenous use, the total concentration of solutes should be controlled in order to render the preparation isotonic.

The present invention also encompasses a pharmaceutical composition useful in the treatment of cancer, comprising the administration of a therapeutically effective amount of the compounds of this invention, with or without pharmaceutically acceptable carriers or diluents. Suitable compositions of this invention include aqueous solutions comprising compounds of this invention and pharmacologically acceptable carriers, e.g., saline, at a pH level, e.g., 7.4. The solutions may be introduced into a patient's intramuscular blood-stream by local bolus injection.

When a compound according to this invention is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual patient, as well as the severity of the patient's symptoms.

In one exemplary application, a suitable amount of compound is administered to a mammal undergoing treatment for cancer. Administration occurs in an amount between about 0.1 mg/kg of body weight to about 60 mg/kg of body weight per day, preferably of between 0.5 mg/kg of body weight to about 40 mg/kg of body weight per day.

The compounds of the instant invention are also useful as a component in an assay to rapidly determine the presence and quantity of farnesyl-protein transferase (FPTase) in a composition. Thus the composition to be tested may be divided and the two portions contacted with mixtures which comprise a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate and, in one of the mixtures, a compound of the instant invention. After the assay mixtures are incubated for an sufficient period of time, well known in the art, to allow the FPTase to farnesylate the substrate, the chemical content of the assay mixtures may be determined by well known immunological, radiochemical or chromatographic techniques. Because the compounds of the instant invention are selective inhibitors of FPTase, absence or quantitative reduction of the amount of substrate in the assay mixture without the compound of the instant invention relative to the presence of the unchanged substrate in the assay containing the instant compound is indicative of the presence of FPTase in the composition to be tested.

It would be readily apparent to one of ordinary skill in the art that such an assay as described above would be useful in identifying tissue samples which contain farnesyl-protein transferase and quantitating the enzyme. Thus, potent inhibitor compounds of the instant invention may be used in an active site titration assay to

determine the quantity of enzyme in the sample. A series of samples composed of aliquots of a tissue extract containing an unknown amount of farnesyl-protein transferase, an excess amount of a known substrate of FPTase (for example a tetrapeptide having a cysteine at the amine terminus) and farnesyl pyrophosphate are incubated for an appropriate period of time in the presence of varying concentrations of a compound of the instant invention. The concentration of a sufficiently potent inhibitor (i.e., one that has a Ki substantially smaller than the concentration of enzyme in the assay vessel) required to inhibit the enzymatic activity of the sample by 50% is approximately equal to half of the concentration of the enzyme in that particular sample.

EXAMPLES

Examples provided are intended to assist in a further understanding of the invention. Particular materials employed, species and conditions are intended to be further illustrative of the invention and not limitative of the reasonable scope thereof.

EXAMPLE 1

N-(3-chlorophenyl)-*N'*-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N'*-(*n*-pentyl)urea hydrochloride (1)

Step 1: Preparation of 1-triphenylmethyl-4-(hydroxymethyl)-imidazole (2)

To a solution of 4-(hydroxymethyl)imidazole hydrochloride (35 g) in 250 mL of dry DMF at room temperature was added triethylamine (90.6 mL). A white solid precipitated from the solution. Chlorotriphenylmethane (76.1 g) in 500 mL of DMF was added dropwise. The reaction mixture was stirred for 20 hours, poured over ice, filtered, and washed with ice water. The resulting product was

slurried with cold dioxane, filtered, and dried *in vacuo* to provide **2** as a white solid which was sufficiently pure for use in the next step.

<u>Step 2:</u> Preparation of 1-triphenylmethyl-4-(acetoxymethyl)-imidazole (3)

Alcohol **2** (prepared above) was suspended in 500 mL of pyridine. Acetic anhydride (74 mL) was added dropwise, and the reaction was stirred for 48 hours during which it became homogeneous. The solution was poured into 2 L of EtOAc, washed with water (3 x 1 L), 5% aq. HCl soln. (2 x 1 L), sat. aq. $NaHCO_3$, and brine, then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product. The acetate **3** was isolated as a white powder (85.8 g) which was sufficiently pure for use in the next step.

<u>Step 3:</u> Preparation of 1-(4-cyanobenzyl)-5-(acetoxymethyl)imidazole hydrobromide (4)

A solution of **3** (85.8 g) and α-bromo-*p*-tolunitrile (50.1 g) in 500 mL of EtOAc was stirred at 60 °C for 20 hours, during which a pale yellow precipitate formed. The reaction was cooled to room temperature and filtered to provide the solid imidazolium bromide salt. The filtrate was concentrated *in vacuo* to a volume 200 mL, reheated at 60 °C for two hours, cooled to room temperature, and filtered again. The filtrate was concentrated *in vacuo* to a volume 100 mL, reheated at 60 °C for another two hours, cooled to room temperature, and concentrated *in vacuo* to provide a pale yellow solid. All of the solid material was combined, dissolved in 500 mL of methanol, and warmed to 60 °C. After two hours, the solution was reconcentrated *in vacuo* to provide a white solid which was triturated with hexane to remove soluble materials. Removal of residual solvents *in vacuo* provided the titled product hydrobromide as a white solid (50.4 g, 89% purity by HPLC) which was used in the next step without further purification.

<u>Step 4:</u> Preparation of 1-(4-cyanobenzyl)-5-(hydroxymethyl)-imidazole (5)

To a solution of the acetate **4** (50.4 g) in 1.5 L of 3:1 THF/water at 0 °C was added lithium hydroxide monohydrate (18.9 g). After one hour, the reaction was concentrated *in vacuo*, diluted with EtOAc (3 L), and washed with water, sat. aq. $NaHCO_3$ and brine. The solution was then dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude product (26.2 g) as a pale yellow fluffy solid which was sufficiently pure for use in the next step without further purification.

Step 5: Preparation of 1-(4-cyanobenzyl)-5-imidazole-carboxaldehyde (6)

To a solution of the alcohol **5** (21.5 g) in 500 mL of DMSO at room temperature was added triethylamine (56 mL), then SO_3-pyridine complex (40.5 g). After 45 minutes, the reaction was poured into 2.5 L of EtOAc, washed with water (4 x 1 L) and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the aldehyde **6** (18.7 g) as a white powder which was sufficiently pure for use in the next step without further purification.

Step 6: Preparation of 1-(4-cyanobenzyl)-5-(*n*-pentylamino-methyl)imidazole (7)

To a solution of the aldehyde **6** (132 mg) in 3 mL of 1,2-dichloroethane at 0 °C was added 4Å powdered molecular sieves (300 mg), *n*-pentylamine (0.217 mL), and sodium triacetoxyborohydride (260 mg). After five days, the reaction was poured into EtOAc and washed with water, sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the amine **7** as a brown oil which was used in the next step without further purification.

Step 7: Preparation of *N*-(3-chlorophenyl)-*N'*-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N'*-(*n*-pentyl)urea hydrochloride (1)

To a solution of the amine **7** (prepared above) in 2 mL of dry DMF at 0 °C was added NaH (37 mg, 60% dispersion in mineral oil). The solution was warmed to room temperature for 10 minutes,

then recooled to 0 °C. 3-Chlorophenylisocyanate (0.084 mL) was added dropwise, and the cooling bath was removed. After three hours, the reaction was poured into EtOAc/hexane (2:1) and water, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide the crude urea **1** as a yellow foam. Half of this material was purified by silica gel chromatography (3-5% $MeOH/CH_2Cl_2$), taken up in CH_2Cl_2 and treated with 1 M HCl/ether solution, and concentrated *in vacuo*. The product hydrochloride **1** (75 mg) was isolated as a yellow solid.

FAB mass spectrum m/e 436 (M+1).
Analysis calculated for $C_{24}H_{26}ClN_5O$ • 1.00 HCl • 1.10 H_2O:
C, 58.56; H, 5.98; N, 14.23;
Found: C, 58.58; H, 6.14; N, 13.26.

EXAMPLE 2

N-(3-chlorophenyl)-*N*-methyl-*N'*-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N'*-(*n*-pentyl)urea hydrochloride (**8**)

To a solution of urea **1** (remaining half of crude product prepared above) in 1 mL of dry DMF at 0 °C was added NaH (14 mg, 60% dispersion in mineral oil). After 15 minutes, iodomethane (0.029 mL) was added dropwise. The reaction was stirred at 0 °C for four hours, then poured into EtOAc/hexane (2:1) and water, washed with sat. aq. $NaHCO_3$ and brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to provide a purple oil. This material was purified by silica gel chromatography (2-5% $MeOH/CH_2Cl_2$), taken up in CH_2Cl_2 and treated with 1 M HCl/ether solution, and concentrated *in vacuo*. The product hydrochloride **8** (22 mg) was isolated as a yellow solid.

FAB mass spectrum m/e 450 (M+1).
Analysis calculated for $C_{25}H_{28}ClN_5O$ • 1.20 HCl • 1.60 H_2O:
C, 57.46; H, 6.25; N, 13.40;

Found: C, 57.52; H, 6.27; N, 12.55.

EXAMPLE 3

In vitro inhibition of ras farnesyl transferase

Assays of farnesyl-protein transferase. Partially purified bovine FPTase and Ras peptides (Ras-CVLS, Ras-CVIM and Ras-CAIL) were prepared as described by Schaber et al., J. Biol. Chem. 265:14701-14704 (1990), Pompliano, et al., Biochemistry 31:3800 (1992) and Gibbs et al., PNAS U.S.A. 86:6630-6634 (1989), respectively. Bovine FPTase was assayed in a volume of 100 μl containing 100 mM *N*-(2-hydroxy ethyl) piperazine-*N'*-(2-ethane sulfonic acid) (HEPES), pH 7.4, 5 mM $MgCl_2$, 5 mM dithiothreitol (DTT), 100 mM [^{3}H]-farnesyl diphosphate ([^{3}H]-FPP; 740 CBq/mmol, New England Nuclear), 650 nM Ras-CVLS and 10 μg/ml FPTase at 31°C for 60 min. Reactions were initiated with FPTase and stopped with 1 ml of 1.0 M HCL in ethanol. Precipitates were collected onto filter-mats using a TomTec Mach II cell harvestor, washed with 100% ethanol, dried and counted in an LKB β-plate counter. The assay was linear with respect to both substrates, FPTase levels and time; less than 10% of the [^{3}H]-FPP was utilized during the reaction period. Purified compounds were dissolved in 100% dimethyl sulfoxide (DMSO) and were diluted 20-fold into the assay. Percentage inhibition is measured by the amount of incorporation of radioactivity in the presence of the test compound when compared to the amount of incorporation in the absence of the test compound.

Human FPTase was prepared as described by Omer et al., Biochemistry 32:5167-5176 (1993). Human FPTase activity was assayed as described above with the exception that 0.1% (w/v) polyethylene glycol 20,000, 10 μM $ZnCl_2$ and 100 nM Ras-CVIM were added to the reaction mixture. Reactions were performed for 30 min., stopped with 100 μl of 30% (v/v) trichloroacetic acid (TCA) in ethanol and processed as described above for the bovine enzyme.

The compounds of the instant invention described in Examples 1 and 2 were tested for inhibitory activity against human FPTase by the assay described above and were found to have IC_{50} of < 10 μM.

EXAMPLE 4

In vivo ras farnesylation assay

The cell line used in this assay is a v-ras line derived from either Rat1 or NIH3T3 cells, which expressed viral Ha-ras p21. The assay is performed essentially as described in DeClue, J.E. et al., Cancer Research 51:712-717, (1991). Cells in 10 cm dishes at 50-75% confluency are treated with the test compound (final concentration of solvent, methanol or dimethyl sulfoxide, is 0.1%). After 4 hours at 37°C, the cells are labelled in 3 ml methionine-free DMEM supplemeted with 10% regular DMEM, 2% fetal bovine serum and 400 mCi[^{35}S]methionine (1000 Ci/mmol). After an additional 20 hours, the cells are lysed in 1 ml lysis buffer (1% NP40/20 mM HEPES, pH 7.5/5 mM $MgCl_2$/1mM DTT/10 mg/ml aprotinen/2 mg/ml leupeptin/2 mg/ml antipain/0.5 mM PMSF) and the lysates cleared by centrifugation at 100,000 x g for 45 min. Aliquots of lysates containing equal numbers of acid-precipitable counts are bought to 1 ml with IP buffer (lysis buffer lacking DTT) and immunoprecipitated with the ras-specific monoclonal antibody Y13-259 (Furth, M.E. et al., J. Virol. 43:294-304, (1982)). Following a 2 hour antibody incubation at 4°C, 200 ml of a 25% suspension of protein A-Sepharose coated with rabbit anti rat IgG is added for 45 min. The immunoprecipitates are washed four times with IP buffer (20 nM HEPES, pH 7.5/1 mM EDTA/1% Triton X-100.0.5% deoxycholate/0.1%/SDS/0.1 M NaCl) boiled in SDS-PAGE sample buffer and loaded on 13% acrylamide gels. When the dye front reached the bottom, the gel is fixed, soaked in Enlightening, dried and autoradiographed. The intensities of the bands corresponding to farnesylated and nonfarnesylated ras proteins are compared to determine the percent inhibition of farnesyl transfer to protein.

EXAMPLE 5

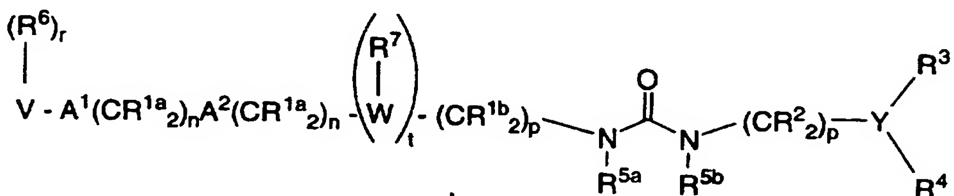
In vivo growth inhibition assay

To determine the biological consequences of FPTase inhibition, the effect of the compounds of the instant invention on the anchorage-independent growth of Rat1 cells transformed with either a v-*ras*, v-*raf*, or v-*mos* oncogene is tested. Cells transformed by v-Raf and v-Mos maybe included in the analysis to evaluate the specificity of instant compounds for Ras-induced cell transformation.

Rat 1 cells transformed with either v-ras, v-raf, or v-mos are seeded at a density of 1 x 10^4 cells per plate (35 mm in diameter) in a 0.3% top agarose layer in medium A (Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum) over a bottom agarose layer (0.6%). Both layers contain 0.1% methanol or an appropriate concentration of the instant compound (dissolved in methanol at 1000 times the final concentration used in the assay). The cells are fed twice weekly with 0.5 ml of medium A containing 0.1% methanol or the concentration of the instant compound. Photomicrographs are taken 16 days after the cultures are seeded and comparisons are made.

WHAT IS CLAIMED IS:

1. A compound which inhibits farnesyl-protein transferase of the formula I:



I

wherein:

R^{1a}, R^{1b} and R^2 are independently selected from:

a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)NR^8$-,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocyclic, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, $-N(R^8)_2$, or $R^9OC(O)$-NR^8-;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $CF_3(CH_2)_nO$-, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^{5a} and R^{5b} are independently selected from:

a) hydrogen,
b) unsubstituted or substituted aryl,

c) unsubstituted or substituted heterocyclic,
d) unsubstituted or substituted C_3-C_{10} cycloalkyl, and
e) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-C(NH)-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:
a) hydrogen,
b) aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $R^8{}_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, C_3-C_{10} cycloalkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NH$-, CN, H_2N-C(NH)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^8OC(O)NH$-;

R^7 is selected from:
a) hydrogen,
b) C_2-C_6 alkenyl, C_2-C_6 alkynyl, perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-C-(NR^8)-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and
c) C_1-C_6 alkyl unsubstituted or substituted by perfluoroalkyl, F, Cl, Br, R^8O-, $R^9S(O)_m$-, $R^8C(O)NR^8$-, CN, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, N_3, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, -C(O)NR^8-, -NR^8C(O)-, O, -N(R^8)-, -$S(O)_2$N(R^8)-, -N(R^8)$S(O)_2$-, or $S(O)_m$;

V is selected from:

a) hydrogen,
b) heterocycle,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl,

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

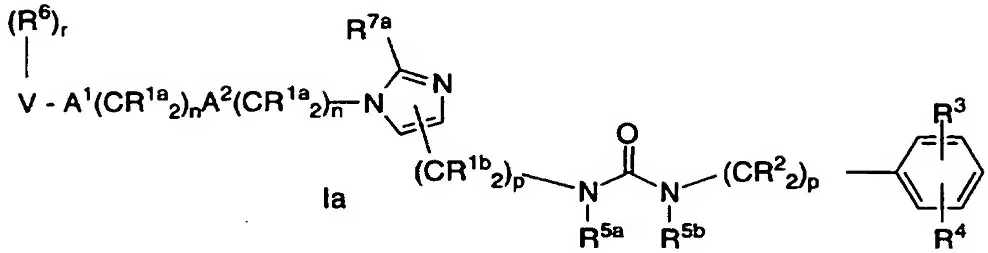
W is a heterocycle;

Y is aryl or heteroaryl;

m is	0, 1 or 2;
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
r is	0 to 5, provided that r is 0 when V is hydrogen; and
t is	0 or 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

2. A compound which inhibits farnesyl-protein transferase of the formula Ia:



Ia

wherein:

R^{1a} and R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, $-N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or $-N(R^8)_2$;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^{5a} and R^{5b} are independently selected from:

a) hydrogen,
and
b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-,

$(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-C(NH)-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^{7a} is hydrogen or methyl;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^8$-, O, $-N(R^8)$-, or $S(O)_m$;

V is selected from:

a) hydrogen,

b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,

c) aryl,

d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and

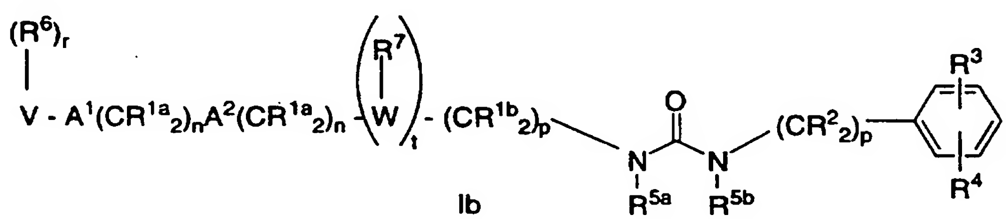
e) C_2-C_{20} alkenyl, and

provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

m is	0, 1 or 2;
n is	0, 1, 2, 3 or 4;
p is	0, 1, 2, 3 or 4;
r is	0 to 5, provided that r is 0 when V is hydrogen; and

or an optical isomer or pharmaceutically acceptable salt thereof.

3. A compound which inhibits farnesyl-protein transferase of the formula Ib:



Ib

wherein:

R^{1a} and R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, $-N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or $-N(R^8)_2$;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or

unsubstituted aryl and substituted or unsubstituted heterocycle;

R^{5a} and R^{5b} are independently selected from:

a) hydrogen,

and

b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:

a) hydrogen,

b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, $-N(R^8)_2$, or $R^9OC(O)NR^8$-;

R^7 is selected from: hydrogen and C_1-C_6 alkyl;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

A^1 and A^2 are independently selected from: a bond, -CH=CH-, -C≡C-, -C(O)-, $-C(O)NR^8$-, O, $-N(R^8)$-, or $S(O)_m$;

V is selected from:

a) hydrogen,
b) heterocycle selected from pyrrolidinyl, imidazolyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, isoquinolinyl, and thienyl,
c) aryl,
d) C_1-C_{20} alkyl wherein from 0 to 4 carbon atoms are replaced with a a heteroatom selected from O, S, and N, and
e) C_2-C_{20} alkenyl, and

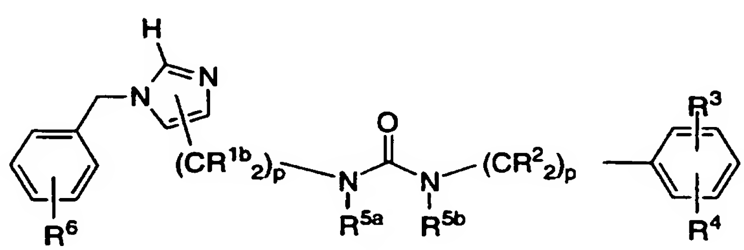
provided that V is not hydrogen if A^1 is $S(O)_m$ and V is not hydrogen if A^1 is a bond, n is 0 and A^2 is $S(O)_m$;

W is a heterocycle selected from pyrrolidinyl, pyridinyl, thiazolyl, pyridonyl, 2-oxopiperidinyl, indolyl, quinolinyl, or isoquinolinyl;

m is 0, 1 or 2;
n is 0, 1, 2, 3 or 4;
p is 0, 1, 2, 3 or 4;
r is 0 to 5, provided that r is 0 when V is hydrogen; and
t is 1;

or an optical isomer or pharmaceutically acceptable salt thereof.

4. The compound according to Claim 1 of the formula Ic:



Ic

wherein:

R^{1b} is independently selected from:

a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or -$N(R^8)_2$;

R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^{5a} and R^{5b} are independently selected from:

a) hydrogen,
and
b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-$C(NH)$-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^6 is independently selected from:

a) hydrogen,
b) C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_1-C_6 perfluoroalkyl, F, Cl, R^8O-, $R^8C(O)NR^8$-, CN, NO_2, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-, and

c) C_1-C_6 alkyl substituted by C_1-C_6 perfluoroalkyl, R^8O-, $R^8C(O)NR^8$-, $(R^8)_2N$-$C(NR^8)$-, $R^8C(O)$-, $R^8OC(O)$-, -$N(R^8)_2$, or $R^9OC(O)NR^8$-;

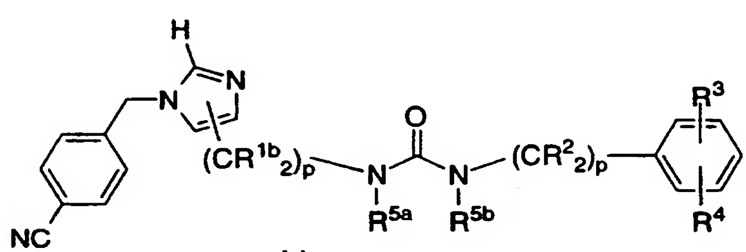
R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

R^9 is independently selected from C_1-C_6 alkyl and aryl;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

or an optical isomer or pharmaceutically acceptable salt thereof.

5. The compound according to Claim 4 of the formula Id:



Id

wherein:

R^{1b} is independently selected from:
a) hydrogen,
b) aryl, heterocycle, cycloalkyl, R^8O-, -$N(R^8)_2$ or C_2-C_6 alkenyl,
c) C_1-C_6 alkyl unsubstituted or substituted by aryl, heterocycle, cycloalkyl, alkenyl, R^8O-, or -$N(R^8)_2$;

R^2 are independently selected from: hydrogen or C_1-C_6 alkyl;

R^3 and R^4 are independently selected from F, Cl, Br, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-C(NH)-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN, $(R^9)OC(O)NR^8$-, C_1-C_{20} alkyl, substituted or unsubstituted aryl and substituted or unsubstituted heterocycle;

R^{5a} and R^{5b} are independently selected from:
a) hydrogen,
and
b) C_1-C_6 alkyl substituted with hydrogen or a group selected from unsubstituted or substituted aryl, unsubstituted or substituted heterocyclic, unsubstituted or substituted C_3-C_{10} cycloalkyl, $N(R^8)_2$, CF_3, NO_2, $(R^8)O$-, $(R^9)S(O)_m$-, $(R^8)C(O)NH$-, H_2N-C(NH)-, $(R^8)C(O)$-, $(R^8)OC(O)$-, N_3, CN $(R^9)OC(O)NR^8$-;

R^8 is independently selected from hydrogen, C_1-C_6 alkyl, benzyl and aryl;

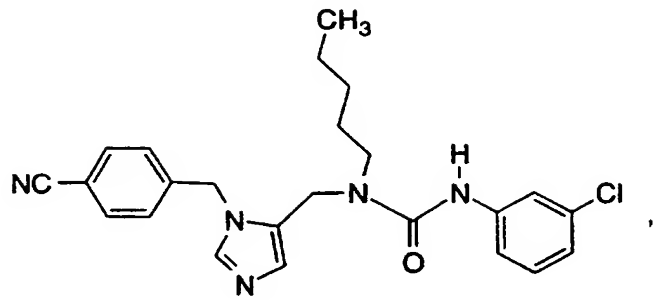
R^9 is independently selected from C_1-C_6 alkyl and aryl;

m is 0, 1 or 2; and
p is 0, 1, 2, 3 or 4;

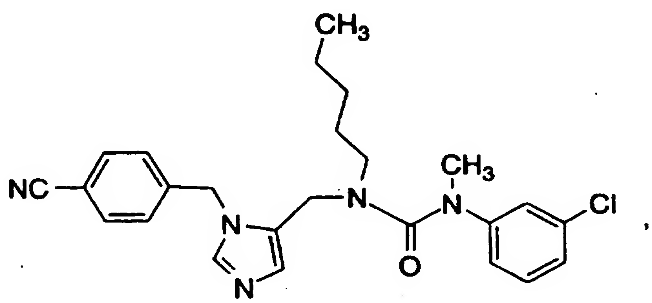
or an optical isomer or pharmaceutically acceptable salt thereof.

6. A compound which inhibits farnesyl-protein transferase which is selected from:

N-(3-chlorophenyl)-*N'*-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N'*-(*n*-pentyl)urea hydrochloride (**1**)



N-(3-chlorophenyl)-*N*-methyl-*N'*-[1-(4-cyanobenzyl)-5-imidazolylmethyl]-*N'*-(*n*-pentyl)urea hydrochloride (**8**)



or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 1.

8. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 2.

9. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 3.

10. A pharmaceutical composition comprising a pharmaceutical carrier, and dispersed therein, a therapeutically effective amount of a compound of Claim 6.

11. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

12. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

13. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

14. A method for inhibiting farnesyl-protein transferase which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

15. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

16. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 8.

17. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 9.

18. A method for treating cancer which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 10.

19. A method for treating neurofibromen benign proliferative disorder which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

20. A method for treating blindness related to retinal vascularization which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

21. A method for treating infections from hepatitis delta and related viruses which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

22. A method for preventing restenosis which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

23. A method for treating polycystic kidney disease which comprises administering to a mammal in need thereof a therapeutically effective amount of a composition of Claim 7.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/01599

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A01N 47/28, 61/00; A61K 31/00, 31/17, 31/41
US CL :514/385, 396, 482, 588; 564/1, 48
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/385, 396, 482, 588; 564/1, 48

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4,576,957 (MARSICO, JR. et al.) 18 March 1986 (18.03.86), see entire document, especially, columns 1, 2, 5, and 6.	1-4, 7-9, 11-13, 15-17, 19-23
A	WO 95/10516 A1 (SCHERING CORPORATION) 20 April 1995 (20.04.95), see entire document.	1-23
A	WO 95/09001 A1 (MERCK & CO., INC.) 06 APRIL 1995 (06.04.95), see entire document.	1-23
A	EP 0 675 112 A1 (BRISTOL-MYERS SQUIBB COMPANY) 04 OCTOBER 1995 (04.10.95), see entire document.	1-23

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 APRIL 1997	14 MAY 1997

Name and mailing address of the ISA/US	Authorized officer
Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	MICHAEL D. PAK
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US97/01599

B. FIELDS SEARCHED
Electronic data bases consulted (Name of data base and where practicable terms used):

APS, STN, BIOSCIENCE, CAPLUS, MEDLINE, EMBASE, SCISEARCH, REGISTRY

search terms: urea, fanesyl transferase, inhibit?, antagoni?